REMARKS

Applicants have amended the specification to correct inadvertent typographical errors in the references to SEQ ID NOs and mis-numbering of the tables. Applicants maintain that the amendments add no new matter.

Applicants have cancelled Claims 22-26, without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 33 to depend from claim 27. Applicants have added new claims incorporating additional limitations of the claimed polypeptide. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the new claims can be found in the substitute specification at page 44, lines 16-21, page 70, lines 30-34, and page 32, line 31 through page 33, line 34.

New Claims 35-45 have been added, thus Claims 27-45 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed March 19, 2004. For the reasons set forth below, Applicants respectfully traverse.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The PTO concedes that the cited utilities are credible. However, the PTO alleges that the invention lacks both substantial and specific utility. Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly

is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

The PTO argues that the invention lacks substantial utility because the evidence in the specification that the level of overexpression in cancer cells of the nucleic acid which encodes the PRO539 protein was minimal, and there is no evidence that overexpression is significant or a real effect and not simply produced by chance. In addition, the PTO argues that the invention lacks utility because the overexpression of the nucleic acid is not relevant to the utility of the protein and there is no evidence that the protein is overexpressed. The PTO cites three references to support its position that there is no necessary correlation between nucleic acid expression and protein expression. Thus, the PTO concludes that because there is no necessary connection between the level of protein in a cell and the amount of mRNA, and no necessary connection between the amount of DNA in a cell and the amount of mRNA, any evidence of overexpression of one component does not provide utility for the protein. The PTO argues that the current situation closely tracks Example 12 of the Utility Guidelines, because where there is no necessary relationship between the protein levels or utilities and a small level of mRNA overexpression in cancer cells, the invention lacks any "real world" context of use for PRO539.

Applicants first address the PTO's argument that the level of overexpression of nucleic acid encoding PRO539 was minimal and insignificant. Applicants submit that the gene amplification data provided in the present application are sufficient to establish a specific and substantial utility for the PRO539 polypeptide.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 16 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 7 (Table 8 as amended herein, page 114 of the substitute specification). As a negative control, DNA was isolated from the blood of normal healthy individuals (page 108, lines 29-31 of the substitute specification). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 7 (Table 8 as amended herein). As explained in the substitute specification on page 109, lines 1-3, the results of TaqMan™ PCR are reported in ΔCt units. It is well-known in the art that "Ct" stands for "threshold cycle." One Ct unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification.

It is well-known in the art how ΔCt values are calculated. The TaqMan™ real-time PCR method, which is the used in the methods of the present application, has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The TaqMan™ 7700 Sequence Detector Software calculates the Ct values for each given experiment. Those of skill in the art know that to obtain ΔCt, the difference between the Ct values of the test sample and the normal sample is calculated. Furthermore, the specification itself teaches that "The diluted samples were used provided that the CT value of the normal human DNA subtracted from test DNA was +/- 1 Ct" (substitute specification at page 113, lines 29-30). Thus, the specification teaches that ΔCt is obtained when the Ct value of the normal sample is subtracted from the Ct value of the test sample.

As for the significance of the data, the specification states that one ΔCt unit corresponds to two-fold amplification, two units to four-fold, three units to 8-fold, etc. This fact is also well-known in the art. Thus, the significance of knowing the ΔCt value is that the extent of gene amplification in a cancer cell is known.

In support of Applicants' assertion of utility, Applicants submit herewith a copy of the declaration of Dr. Audrey Goddard with exhibits A-G (the Goddard Declaration), originally submitted in a related and co-owned patent application Serial No. 09/903,925. As Dr. Goddard's *curriculum vitae*, Exhibit A of the Goddard Declaration, shows, she is an expert in the art of identifying and quantifying the amplification of oncogenes in cancers.

In her declaration, Dr. Goddard states that

> the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

The Goddard Declaration, paragraph 7. Therefore, according to Dr. Goddard, a 2-fold increase, i.e., a ΔCt value of 1, not only is not of questionable significance, but is "significant and useful"

in, *inter alia*, detecting cancerous tumors or the diagnosis of cancer. Thus, the Goddard Declaration support Applicants' position that the ΔCt value of 1 or more is significant and is outside of the experimental error of this procedure. As is indicated in Table 7 (Table 8 as amended herein), the ΔCt value for PRO539 is greater than 1 for several tumor cell types, indicating a more than 2-fold amplification.

This argument along with the Goddard Declaration was presented to Examiner Fredman in the closely related and co-owned patent application Serial No. 10/033,167 to overcome a nearly identical 35 U.S.C. § 101 utility rejection. That closely related application is directed in part to the nucleic acid sequence encoding the PRO539 protein and contains the same data presented and relied on in the instant application. In that case, the PTO concluded that the Goddard declaration was "sufficient to overcome the rejection of the claims based upon utility and enablement as discussed above." (Office Action dated 9/9/2003, page 5, paragraph 8).

Applicant next addresses the PTO's argument that there is no necessary correlation between level of protein in a cell and the amount of nucleic acid. Citing three references, the PTO correctly states that increased gene copy number does not *necessarily* result in increased protein expression. The standard for utility is not, however, absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. The fact that in specific cases there seemed to be no correlation between gene amplification and the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. The PTO has not shown whether the lack of correlation observed in the cited references is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Enclosed is a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration was submitted in connection with co-pending application Serial No. 10/006,867. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." The references cited in the declaration and submitted herewith support this statement.

Pursuant to 37 C.F.R. § 1.132, Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, such as those cited by the PTO, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6). Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between an increase in gene expression and the level of the encoded protein.

As discussed above, the data presented in Table 7 (Table 8 as amended herein) on page 114 of the substitute specification indicate ΔCt values for the DNA encoding the PRO539 polypeptide of greater than 1, which mean at least a 2-fold increase in gene copy number in tumor tissue samples as compared to normal tissue samples. Using a widely accepted technique, Applicants have generated data showing that the gene encoding the PRO539 polypeptide is amplified in cancerous tissue. The general, accepted understanding in the art is that the level of protein expression would therefore also be increased.

Applicants believe they have supplied sufficient evidence to show that there is a significant correlation between gene amplification and protein expression. However, even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. Enclosed is a copy of a Declaration by Avi Ashkenazi, an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925.

As explained in paragraph 6 of the Ashkenazi Declaration:

> Even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

This statement is echoed by Mr. Grimaldi in his declaration at paragraph 6.

As set forth on page 83, lines 17-20 of the substitute specification, the disclosed proteins of the invention can be used for tissue typing. In addition, as indicated on page 88, lines 3-5 of the substitute specification, the disclosed proteins can be used to generate antibodies to PRO539. Table 7 (Table 8 as amended herein) identifies several tissue types, all obtained from cancerous tumors, in which PRO539 nucleic acids are amplified. As a result, PRO539 nucleic acids, polypeptides, and antibodies can be used diagnostically in determining whether a particular tissue type obtained from a patient is cancerous or not, and to more accurately determine the type of tumor. Thus, those of skill in the art recognize the substantial utility of the PRO539 polypeptide as a diagnostic and therapeutic tool.

Specific Utility

The PTO argues that even if substantial utility were found, there is no specific utility given for the PRO539 protein, since the protein, as distinguished from the nucleic acid, has not been associated with any disease, condition, or any other specific feature. Relying on the lack of correlation between levels of nucleic acid and protein cited in the Gokman-Polar and Meric references, the PTO argues that the overexpression of the nucleic acid gives no specific utility because it is entirely unrelated to uses of the protein. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. 2107.01 I. Applicants submit that the evidence of overexpression of PRO539 nucleic acids in certain types of cancer cells along with the declarations discussed above provide a specific utility for the claimed proteins. As stated above, the general, accepted understanding in the art is that the level of protein expression would be increased, and thus there is a correlation

between nucleic acid levels and protein levels. This makes the PRO539 protein useful in diagnosing and further characterizing cancer as well as developing antibodies for use in the same. As stated above, even if protein levels are not increased, the PRO539 proteins are still useful in further characterizing the type of tumor. All of the substantial utilities listed above are specific to the disclosed PRO539 proteins because there is evidence that PRO539 is overexpressed in certain cancer cells compared to normal cells. This is not a general utility that would apply to the broad class of proteins.

The overexpression of PRO539 nucleic acid in certain cancer cells distinguishes this case from Examples 4 and 12 of the Utility Guidelines cited by the PTO. In both examples, there is no description of the protein beyond its sequence or its binding of an unidentified ligand. Here, the disclosed proteins are encoded by a nucleic acid that is overexpressed in certain cancer cells. This makes the utility of using the protein to diagnose and type cancer cells specific, since in general, proteins are not encoded by nucleic acids which are overexpressed in cancer cells.

Conclusion

Applicants have provided several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, Drs. Goddard, Polakis, and Ashkenazi, and must treat as true the statements made by these experts. Applicant reminds the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Thus, given the totality of the evidence provided, Applicants submit that they have established a specific and substantial credible utility for the claimed polypeptide as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the PRO539 polypeptide set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Written Description

The PTO rejected Claims 22-26, 33 and 34 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The PTO states that "the compound is claimed solely [by] its protein sequence related 80%-99% SEQ ID NO: 7 without any correlative function to delimit the structure." The Office Action at page 9, lines 2-4. The PTO argues that at the time of filing there is no record or description which would demonstrate conception of any proteins other than those expressly disclosed which comprise SEQ ID NO: 7.

Applicants respectfully disagree. However, in order to further clarify the functional limitations shared by the polypeptides of the invention, and in order to advance the case towards allowance, Applicants have cancelled Claims 22-26, and amended Claim 33. New Claims 35-49 incorporate additional limitations to further delimit the structure of the claimed polypeptides by providing a functional limitation which is correlated to the structure of the polypeptide or limiting any amino acid substitutions to conservative substitutions as defined in the specification. In view of the additional limitations, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112 – Enablement

The PTO rejected Claims 22-34 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The PTO correctly cites *In re Wands* and the factors set forth therein to determine the scope of enablement. However, Applicants respectfully submit that the PTO's conclusions are not in line with the teachings of *Wands*.

For example, given the recent advances in the science of molecular biology, the unpredictability of this art has lessened significantly. As a result, the number of experiments necessary to determine a particular result is now low, and these experiments have become routine in the art. The PTO concedes that the level of skill in this art is very high, and thus ordinary artisans are expected to be adept in various methodologies in this art and practice them routinely.

The Applicants believe that the arguments and declarations discussed above make clear that evidence of overexpression of the PRO539 gene in cancer is significant, and that the general understanding of those of skill in the art would be that the PRO539 proteins have a specific and substantial use in the diagnosis and characterization of cancer cells. This would include, for example, the use of PRO539 proteins as immunizing agents to create antibodies for the diagnosis of cancer or further characterization of cancer cells. Use of the proteins as an immunizing agent is disclosed in the application, for example at page 88, lines 4-5 of the substitute specification, and the techniques for the creation of antibodies are well known and routine in the art. Thus, at least one use of PRO539 protein is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention" (M.P.E.P. 2164.01(c)). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: June 16, 2004

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